Alteplase for stroke: money and optimistic claims buttress the "brain attack" campaign

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Both doctors and the public are becoming more alert to potential conflicts of interest, and an increasing number of journals now require competing interest statements from their authors and reviewers. In this article Jeanne Lenzer uses the example of guidelines produced by the American Heart Association to discuss some of the questions that can arise when interests conflict

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As doctors and the public become more aware of conflicts of interest involving study bias,[1] publication bias,[2] and industry gift giving[3] they turn to credible non-profit organisations for sound medical recommendations. Unfortunately, many groups (and their individual panellists) that serve as arbiters of inconclusive data may also suffer from conflicts of interest.[4 5]

One such conflict is self referencing bias. An example of this is in specialty guidelines for colon cancer screening, where radiologists recommend barium enemas while gastroenterologists recommend colonoscopy. A more important conflict arises when corporations with a financial stake in the recommendations issued by a non-profit making organisation provide financial support for that organisation.

In this paper I examine an example of such a conflict, in which a treatment recommendation that could cost more lives than the disease itself was supported by statistics from only one randomised controlled study. Additionally, poor outcomes and dissenting opinion appear to have been obscured. This recommendation may have been made in a true spirit of unbiased scientific inquiry, but the appearance of dispassionate analysis was eroded by large donations from a drug company to the organisation making the recommendation and payments for research and lecture fees to its individual expert panellists.

Summary points

- The American Heart Association rated the thrombolytic agent alteplase (tPA) as a class I (definitely recommended) intervention for stroke despite controversy about its safety and efficacy
- Most of the association's stroke experts have ties to the manufacturers of alteplase
- Genentech, the US manufacturer of alteplase, contributed over $11m to the American Heart Association in the decade before its recommendation on alteplase
- Following public scrutiny, the American Heart Association recently withdrew statements that alteplase for stroke "saves lives"
- Seemingly impartial organisations that issue professional guidelines may have ties to the manufacturers of recommended interventions

The recommendation and the doubts

In August 2000 the American Heart Association upgraded its recommendation of alteplase (tPA) for stroke from optional (class IIb) to definitely recommended (class I)[6] despite continuing controversy about the safety and efficacy of the treatment. The concerns include the following:

- Most randomised, controlled trials show that thrombolytics increase mortality in acute ischaemic stroke[7–11]
- The recommendation was based on one trial: the National Institute of Neurological Diseases and Stroke (NINDS) trial.[12] In this trial many more patients in 90-180 minute treatment arm had mild stroke scores at baseline, while more in the placebo arm had worse scores (see table)[12]
- The external validity of this particular trial is questionable since the proportion of patients enrolled in the 0-90 minute group was artificially increased through study design criteria[13]
- Chance alone could explain the benefit shown in this single study[8 9 13]
- Efficacy in expert hands is not the same as clinical effectiveness in usual clinical practice[8]
- One fifth of patients initially diagnosed with stroke by expert stroke teams were subsequently found not to have strokes.[14] Exposing such patients to alteplase would incur all the risks with none of the benefit
- Even assuming effectiveness, the clinical impact is marginal, with only 0.4% of patients potentially benefiting from alteplase.[15]

These concerns and others have caused the Canadian Association of Emergency Physicians to conclude, "Further evidence is necessary to support the widespread application of stroke thrombolysis outside

of research settings."[10] The American Academy of Emergency Medicine similarly concluded:"Objective evidence regarding the efficacy, safety, and applicability of tPA for acute ischemic stroke is insufficient to warrant its classification as standard of care.[16] After an urgent request from concerned members,[12] the American College of Emergency Physicians is considering a policy statement that supports a much more restrictive recommendation of alteplase for stroke than represented by the class I recommendation of the American Heart Association. According to college national board member, Susan Nedza, "Leaders in emergency medicine are raising significant scientific, ethical and implementation issues" (personal communication, February, 2001).

Statistics and spin

The American Heart Association first classified alteplase as an optional (class IIb) intervention after the Food and Drug Administration approved its use in ischaemic stroke in 1996. In 2000 alteplase was upgraded to a definitely recommended intervention (class I) after further review of reports after the National Institute of Neurological Diseases and Stroke trial.

Another observational study, the "standard treatment with alteplase to reverse study" (STARS),[17] was favourably considered despite the fact that it had strong ties to the manufacturer of alteplase (all sites were part of the Genentech-sponsored "alteplase thrombolysis for acute noninterventional therapy in ischemic stroke" (ATLANTIS) trials). It was not an "effectiveness" study (since it involved experts who had participated in the prior randomised controlled trials) and it relied on voluntary site reporting (results from 31% of ATLANTIS sites were not included).

Rather strikingly, on the other hand, the association made no mention of the Cleveland area experience,[18] which reported catastrophic results with community use of alteplase for stroke: patients treated with alteplase had twice the death rate of similar patients not treated. Unlike STARS, the Cleveland study had minimal ties to the manufacturer, represented true community practice, and, most important, did not reflect selective reporting, as it included all non-Veterans Administration patients treated for stroke in the city of Cleveland.

Advocates of alteplase have dismissed clinical trials outside of the National Institute of Neurological Diseases and Stroke trial as heterogeneous and note that the American Heart Association guidelines encourage adherence to the protocols of the National Institute of Neurological Diseases and Stroke. However, critics caution that selective emphasis of a single study is scientific folly: "There are numerous examples in medicine where a single small study (or even a few studies) seemed to support a promising hypothesis, but subsequent larger work failed to confirm that benefit (or showed substantial harm)."[13]

More patients treated with alteplase than those treated with placebo had mild strokes at baseline in the 91-180 minute group, while those with the worst strokes were more likely to be in the placebo group. Mean scores overall were also lower at baseline for patients given alteplase

Baseline NIHSS scores	Alteplase (%)	Placebo (%)
0-5	19.0	4.2
>20	18.3	27.5

From table 3.[12]

Verification of data thwarted

Attempts to obtain raw data from the National Institute of Neurological Diseases and Stroke trial or the alteplase thrombolysis for acute noninterventional therapy in ischemic stroke part A trial have been unsuccessful. Drs Clark (ATLANTIS) and Marler (National Institute of Neurological Diseases and Stroke) and Genentech have turned down requests for the raw data. A formal Freedom of Information Act request for the data from the National Institute of Neurological Diseases and Stroke trial has been filed with the Food and Drug Administration, but a preliminary response from the administration's legal counsel was negative.

Making the raw data available for scrutiny seems all the more prudent given that Genentech provided the data monitoring services for the National Institute of Neurological Diseases and Stroke trial. A clinical review by the Food and Drug Administration of a pilot study for the trial indicates that some of Genentech's data calculations were inaccurate: "In calculation of infarct volume … the volumes exceed not only the volume of a cerebral hemisphere, but even the volume of the entire cranial vault."[19]

Although the provision of data monitoring services by Genentech may not have caused data errors, the refusal of the trial investigators to release their raw data and of Genentech to describe the function it fulfilled in providing such services makes data verification impossible. This is of particular interest since some potentially important data (such as primary endpoint mortality at 24 hours) were never published.

Bloated claims: the "brain attack" campaign

In the mid 1990s the American Heart Association launched a major initiative known as the "brain attack" campaign. This term was encouraged so clinicians and patients would think of stroke as an emergency on a par with myocardial infarction, or "heart attack." This campaign rested on the touted value of alteplase.

This is how alteplase for "brain attack" was described in American Heart Association literature[20]: "A clot-busting drug that helped revolutionise heart attack treatment, tPA holds enormous potential for the treatment of ischemic stroke, which accounts for 70 to 80 percent of all strokes. It is estimated that tPA could be used in 400 000 stroke cases per year to save lives, reduce disability and reverse paralysis. Yet tPA is now only being used in some 4000 to 6000 cases annually."

The statement "save lives" is not supported by data from any fibrinolytic trial. No trial has ever shown a reduction in mortality from alteplase use in stroke, but several have shown substantially increased mortality. American Heart Association president, Dr Rose Marie Robertson, withdrew this statement when its inaccuracy was pointed out in conjunction with questions about potential conflicts of interest.[21]

The American Heart Association and potential conflicts of interest

In the late 1990s there were rumours in the medical community that Genentech had paid for the national

headquarters of the American Heart Association. Although some dismissed this as an urban myth, the rumours proved true. Minutes of the American Heart Association board of directors' meeting on 18 October 1991 confirm that Genentech contributed $2.5m (£1.8m, €2.8m) to build the association's headquarters in Dallas. Further research shows that Genentech's contributions to the American Heart Association have totalled $11m (£7.8m, €12.6m) over the past decade.[20 21]

Dr Robertson has argued that Genentech's contributions had no effect on American Heart Association guidelines. She stated that the panellists were "independent" and required to file conflict of interest statements.[21] Since no conflict of interest statements were published with the American Heart Association's *Guidelines 2000*, physicians and the public may reasonably conclude that the association and its panellists were free of competing interests. However, the association will not release the conflict of interest statements for public inspection and verification.

A panel of nine was responsible for the guidelines, eight supporting alteplase and one dissenting. Independent investigation for this article shows that six of the eight panellists who supported alteplase for stroke as a class I recommendation had ties to the manufacturer. Four panellists received lecture fees as members of the Genentech speakers bureau; one serves as a consultant to Boehringer Ingelheim, a "development and marketing partner" with Genentech in producing and distributing alteplase; and two received research funding from Genentech (some panellists had more than one form of relationship with Genentech.) Only two of the panellists who supported the upgraded classification had no ties to the manufacturer. Dr Jerome Hoffman, the lone dissenting panellist, also had no industry ties.

Two panellists initially denied receiving Genentech funding or fees. One, who received lecture fees, acknowledged speaking for Genentech only after being told of evidence of his relationship: "I didn't realise I was *officially* on the speakers bureau." When asked the time frame of his lectures, he responded, "Mostly between 1997 and 2000." Another panellist denied being a principal investigator on a Genentech-sponsored trial, only acknowledging this role after being told that a coauthor had identified him as a principal investigator and after receiving a copy of the original article listing him as such. He said he had enrolled only a few patients, then withdrew from the study and didn't realise his name was listed as a principal investigator in *JAMA*.

Some argue that industry gifts or funding do not usually result in distorted science.[22] However, manufacturers' sponsorship of clinical trials is increasing,[23] and treatment benefits have been shown to be overstated in sponsored trials,[1] while risks are understated,[24] and undesired data are more likely to be suppressed.[25]

Delayed publication, missing data

A single Genentech sponsored trial, alteplase thrombolysis for acute noninterventional therapy in ischemic stroke (ATLANTIS) part A,[26] prospectively replicated many of the methods of the National Institute of Neurological Diseases and Stroke trial, including its enrolment of a subgroup of patients in a 0-3 hour window. (The overall trial measured outcomes with alteplase given 0-6 hours after onset of symptoms.) Part A was negative: alteplase did not improve stroke recovery but did dramatically increase mortality rates (at 30 days 18% of patients given alteplase had died versus 4% of those given placebo). Inclusion of a 0-3 hour subgroup of patients was done, according to lead author Dr Wayne Clark, to "see if we could replicate the results of the National Institute of Neurological Diseases and Stroke [trial]" (personal communication, September 2000). Yet no subgroup analysis of the 0-3 hour cohort was described in the final publication. Furthermore, the results of part A were not published for six years after the trial's completion, even after results from both the National Institute of Neurological Diseases and Stroke trial (conducted concurrently) and a second phase of the same trial (part B) were released.[26]

Dr Clark, responding to an inquiry about the cause of the delayed publication of part A, said; "The investigators asked several times to publish it. I guess the company thought that it might somehow bias the ongoing 3 to 5 hour study [part B]. But I don't have a good answer for you."

Genentech has declined to respond to Dr Clark's statements saying they won't comment on "unsubstantiated rumours" (personal communication, Shelly Schneiderman, Genentech, August, 2001).

Suppressed dissent: the disappearing of Dr Hoffman

Dr Jerome Hoffman, one of the nine experts empanelled by the American Heart Association to develop the guidelines, provided the sole dissent to the organisation's recommendation. The eight other panellists were known to support alteplase for stroke from prior publications. After his expert testimony at the guidelines meeting he was asked by the American Heart Association to provide a written commentary expressing the basis of his dissent. Although he submitted this paper at least a year before the final guidelines were released, it was never published and the guidelines did not mention it. In addition to removing Dr Hoffman's name from the list of authors of the guidelines (at his request), the association also, for unexplained reasons, removed his name from the list of expert panellists.[27] This deprived the scientific community of knowledge about the basis for Dr Hoffman's dissent and it obscured an important signal that any dissent existed at all.

Chameleon ethics

Although a study to verify the outcomes of National Institute of Neurological Diseases and Stroke could benefit the public, it could only harm those who stand to gain financially. A revealing history of such risks comes from Genentech itself. Dr Elliott Grossbard, a Genentech scientist, vigorously opposed a head to head study of alteplase and streptokinase for myocardial infarction. He put Genentech's position bluntly: "We don't know how another trial would turn out. And if we don't come out ahead, we would have a tremendously self-inflicted wound … [another study] may be a good thing for America, but it wasn't going to be a good thing for us."[28]

Although good science has long relied on dissection of prior studies and data verification, this value has been stood on its head in the name of

"ethics" by those with a financial stake in the outcome. Both Dr Clark and Genentech have opposed further studies of alteplase in stroke, stating they would be "unethical" in view of the National Institute of Neurological Diseases and Stroke trial results. Critics point out that another study is crucial regardless of outcome. If benefit is found far greater physician compliance with the American Heart Association guidelines could be expected. If the outcome were negative, it would seem that caution is in order.

Not just Genentech and the American Heart Association

Industry funding of non-profit healthcare and professional organisations is widespread. The attorneys general of 16 states and the Corporation Counsel for Washington, DC issued a report in 1999 about the increasing number of ties between non-profit organisations and pharmaceutical companies. They concluded that the public was given "false and misleading" messages as a result.[29] A few examples of such sponsorships include the American Cancer Society, which is funded by AstraZeneca, Johnson and Johnson, Bristol-Myers Squibb, Eli Lilly, and other manufacturers of diagnostic tests and treatments for prostate cancer. Breast Cancer Awareness Month is funded by AstraZeneca, the manufacturer of Nolvadex (tamoxifen), while Eli Lilly, manufacturer of fluoxetine (Prozac) along with 17 other manufacturers of psychoactive drugs, provided $11.72m (£8.3m, €13.4m) to the National Alliance of the Mentally Ill.

Conclusions

Expert guidelines are expected to be objective, impartial, and independently derived. Sponsorship from organisations that stand to gain from recommendations favourable to their products threatens to undermine such objectivity. Given the profitability of drugs and medical devices, such neutrality is badly needed. Professional societies, particularly those with influence on medical practice, should adopt rigorous standards with regard to industry sponsorship. Such standards should avoid all appearance of potential bias, enabling critical analysis to be conducted in an environment independent of profit motives, providing equal opportunity to test inexpensive therapies with expensive ones, and encouraging open criticism in a forum of dispassionate scientific debate.

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Commentary: Who pays the guideline writers?

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These days everyone is suspicious. This is not surprising, with revelations of donations to political parties for favours, cash for questions in parliament, and auditors in bed with their clients. So we all have to be more regulated—inspection of hospitals, revalidation of doctors, audits of everything in a great bureaucratic sludge of countless copies of countless pieces of paper. We are to be transparently accountable for what

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we do. We cannot be trusted. And now, according to Jeanne Lenzer and a recent paper in *JAMA*,[1] even apparently independent clinical guidelines are suspect.

Increasingly, government encourages universities, and so academic clinicians, to collaborate with industry. But there is a price to pay and a balance to be struck.[2 3] Research is not as independent as it should be. Industry may plan and organise randomised trials, own the data, and analyse and write up the results—though companies may now have trouble publishing them in front line journals.[4] Authors change the wording in their books and papers to suit industry. Companies "place" review papers by their nominated authors in respectable journals. Educational material is written not by who you think but by public relations companies hired by industry. Doctors are flown to tourist destinations to listen to other doctors promoting the company line, with company slides.

Guideline committees necessarily include people with content knowledge. But nowadays, such is their entanglement with commerce, most experts have ties with industry—consultancies, lecture fees, research grants, and even direct interests such as shares.[5 6] All this should be declared, and indeed it may be. But what does a bald statement of a consultancy actually mean? Should it not be quantified? Accepting a ham sandwich may not colour one's attitude, but what about a million pounds, or two million or—in the case of the American Heart Association—$11m?

I have no idea how much money is required to influence guideline writers. But I fear we are going to have to add to the bureaucratic sludge by insisting that they, and any sponsoring organisations, declare just how much they have received from whom to do what. More work, but at least this information can easily be put on appropriate web sites, as the Association of British Neurologists is about to do. Others should follow suit. Even medical charities are not exempt because they too receive industry funding, which may influence their lobbying of government and official organisations such as the National Institute for Clinical Excellence (NICE) for new treatments. Unfortunately, such is the potential for conflict of interest, we all have to be more regulated and, I believe, quantify our interest. Readers can then judge the conflict—how much it takes to make the professor spin a little this way or that.

And what about me? I never found the National Institute of Neurological Diseases and Stroke trial for thrombolysis after acute ischaemic stroke convincing enough to change practice. Only about 600 patients were included. The treated and control groups were not properly balanced at baseline, perhaps by chance or because of problems with the decentralised and complicated randomisation procedure. Furthermore, defining the intention to treat group for analysis was, I now realise, "not a simple issue" (www.fda.gov/cber/products/altergen061896.htm). Even the meta-analysis of all the randomised evidence (5216 patients) is not particularly convincing.[7] So I am involved in another trial, IST-3 (www.dcn.ed.ac.uk/ist3). And I have received a few thousand pounds in consultancy fees from Boehringer-Ingelheim, who make alteplase. From now on I shall be counting just how many pounds—in public.

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Commentary: Thrombolysis in stroke: it works!

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Intravenous tissue plasminogen activator (alteplase, tPA) administered within three hours of the onset of symptoms to appropriate patients with acute ischaemic stroke is a proved treatment of substantial benefit. Data from six trials enrolling patients within three hours show this reality unequivocally (see figure).[1–4] The P value for a beneficial treatment effect is 0.00002, indicating a 1 in 50 000 chance that these findings arise by chance alone. How substantial is alteplase's effect? The absolute risk reduction in poor outcomes is 13.1%. For every 1000 patients treated with alteplase 131 will avoid a poor outcome as a result. The number needed to treat to prevent one poor outcome is less than 8. This benefit is an order of magnitude greater than that of aspirin, the only other pharmacological agent of proved efficacy for ischaemic stroke. Convergent data from three additional trials of streptokinase enrolling stroke patients within three hours of onset, as well as complementary results from a randomised trial of intra-arterially delivered pro-urokinase up to six hours from onset, suggest, but do not yet prove, that this treatment benefit is a class effect of fibrinolytic agents, rather than agent specific.[5]

Recent pooled analysis

These data have been reinforced by a pooled analysis of individual patient data from the six alteplase trials, involving 2776 patients from over 300 hospitals in 18 countries, and fully adjusting for any imbalances in baseline entry characteristics among patients allocated to active treatment and placebo (TG Brott et al, 27th International Stroke Conference, San Antonio, Texas, 2002). The pooled analysis confirms a marked benefit of alteplase in improving the odds of a favourable outcome, graded over time. Between onset and 1.5 hours alteplase treatment increases the odds of favourable outcome by 2.8 (95% confidence interval 1.8 to 9.5) and between 1.5 to 3 hours by 1.5 (1.1 to 2.1).

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Moreover, these data for a simple, dichotomised endpoint underestimate the beneficial impact of alteplase, failing to capture more fine grained, but still clinically meaningful, improvements. For alteplase administered under three hours the number needed to treat to improve by one functional grade on the standard Rankin scale of disability is just 2.[1 6]

You won't find this information in the article by Lenzer in this issue of the *BMJ*. Instead innuendo and misinformation abound. For example, the article repeats the claim that the benefit of fibrinolytic therapy within three hours is supported by data from only a single trial (rather than the actual six), a long exploded myth.[4 7 8] Even the National Institute of Neurological Disorders and Stroke trials consisted of two trials (reported in one article[1]). Lenzer's discussion of delays in publishing the ATLANTIS trials' under three hour results seems to imply that unfavourable data are being hidden. These data have actually been available in preliminary form for two years[7] and have now been published in final form, and they support the therapy's benefit.[3] The article suggests data from the National Institute of Neurological Disorders and Stroke trials were not subject to independent review. In fact, trial data underwent two independent audits, by an autonomous contractor funded by and reporting to the National Institutes of Health (not Genentech) and by the US Food and Drug Administration.

What to do about conflicts of interest

The article does raise important issues about the management of potential conflicts of interest among authors of clinical practice guidelines, albeit in a needlessly inflammatory manner. In 1999 the United States National Institutes of Health spent $17.8bn (£12.5bn, €22.3bn) for research and the top 10 pharmaceutical companies $22.7bn (£16bn, €26bn). When society has decided to rely so greatly on for profit companies to perform clinical research, apparent (and occasionally genuine) conflicts of interest among expert clinical researchers are bound to occur.[9] Indeed, a recent survey by Choudhry et al found that 87% of authors of treatment guidelines in all fields of medicine had some form of interaction with the pharmaceutical industry.[10] The recommendation advanced by Lenzer, that experts "avoid all appearance of potential bias" is presently unworkable and undesirable.[11 12] Such extreme "financial correctness" would leave treatment guideline development largely to individuals who are not experts in the disease being treated[13] and therefore presumably ill equipped to reach reliable conclusions.

In contrast, Choudhry et al have proposed reasonable, immediately implementable recommendations for managing potential conflicts of interest for authors of clinical practice guidelines: (1) disclosure of potential conflicts of interest to other participants at the beginning of the guideline creation process, (2) exclusion of authors with financially substantial conflicts, and (3) complete disclosure of each author's potential conflicts to readers of guidelines.[10]

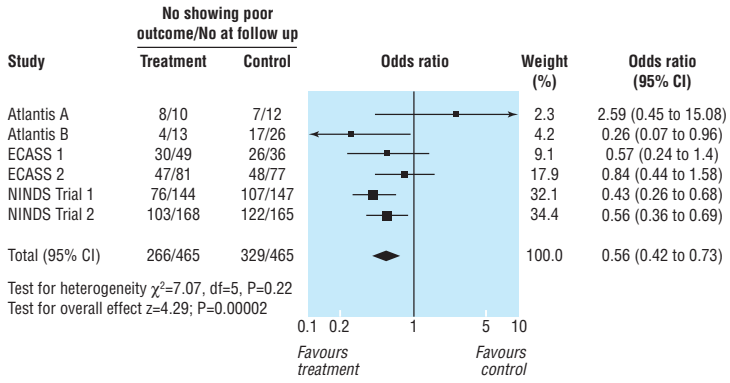
With regard to thrombolysis for stroke, such disclosures will show that some authors of stroke treatment guidelines, including ourselves, and the American Heart Association have received speaking honorariums, research funding, grants, and other support from manufacturers of thrombolytics. If thrombolytics do work in stroke these relationships might indicate a laudatory effort by physician and organisational advocates for stroke patients to channel the self interest of profit making companies to improving stroke care, rather than undue bias. Thrombolytic agents are efficacious in stroke.

What then are *BMJ* readers to make of the article's accusations of bias and poor judgment, given that its central claim that alteplase is an unproved therapy is flawed? Firstly, that medical journals need to be wary, lest claims that might not pass muster scientifically reach their pages under the banner of "investigative journalism."[14] Secondly, acute ischaemic stroke is now a treatable disease. The initial thrombolytic trials have shown biological activity and clinical benefit: early reperfusion can salvage threatened brain tissue and improve patient outcomes. Building on this fundamental breakthrough, current clinical trials in acute stroke are exploring a remarkable variety of novel pharmacological agents, means of drug delivery, combination therapies, mechanical recanalisation techniques, and imaging to optimise patient selection.

The real scandal

Thirdly, and most importantly, the real scandal in acute stroke care is not that thrombolytic therapy is being used, but that it is not being used often or wisely enough.[15] Only 1-2% of acute stroke patients in the US are receiving thrombolytic therapy. Public education campaigns and reorganisation of medical services can substantially increase the proportion of patients treated.[16] Concerns about the everyday effectiveness, as opposed to clinical trial efficacy, of thrombolytic therapy have been raised[15] and constitute a call to action, not resignation.[4 17] While recent reports raised awareness regarding the community use of intravenous alteplase, there are numerous published accounts reporting safety and outcome data which compare favourably with the National Institute of Neurological Disorders and Stroke trials.

Emergency physicians, neurologists, and other professionals caring for acute stroke patients, working in cooperation, can and should master the key elements of thrombolytic care or allow patients to be diverted to specialised acute stroke centres where thrombolytic therapy



Comparison of intravenous alteplase versus placebo controls when given to patients within three hours of onset of stroke. Outcome is poor outcome at end of trial follow up

can be expertly administered.[18] Ideally, as many patients as possible would be treated within 90 or 120 minutes of onset, when benefit is maximal. The time has come for proponents of thrombolysis and reformed thrombolytic contrarians to join together to improve systems of acute stroke care worldwide so that more properly evaluated, properly selected, and properly informed stroke patients can be treated with intravenous thrombolytics within three hours of onset.

JLS, CSK, and SS have served as site investigators in acute stroke clinical trials sponsored by several (15, 11, and 17 respectively) pharmaceutical and biotechnology companies, including Genentech and Boehringer-Ingelheim; have received speaking honorariums from several (12, 5, 8) pharmaceutical companies, including Genentech and Boehringer-Ingelheim; and have served as consultants on scientific advisory boards for several (7, 1, 5) pharmaceutical and biotechnology companies developing acute stroke treaments, including Boehringer-Ingelheim and Genentech.

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Evidence base of clinical diagnosis

Clinical problem solving and diagnostic decision making: selective review of the cognitive literature

Arthur S Elstein, Alan Schwarz

This article reviews our current understanding of the cognitive processes involved in diagnostic reasoning in clinical medicine. It describes and analyses the psychological processes employed in identifying and solving diagnostic problems and reviews errors and pitfalls in diagnostic reasoning in the light of two particularly influential approaches: problem solving[1–3] and decision making.[4–8] Problem solving research was initially aimed at describing reasoning by expert physicians, to improve instruction of medical students and house officers. Psychological decision research has been influenced from the start by statistical models of reasoning under uncertainty, and has concentrated on identifying departures from these standards.

Summary points

- Problem solving and decision making are two paradigms for psychological research on clinical reasoning, each with its own assumptions and methods
- The choice of strategy for diagnostic problem solving depends on the perceived difficulty of the case and on knowledge of content as well as strategy
- Final conclusions should depend both on prior belief and strength of the evidence
- Conclusions reached by Bayes's theorem and clinical intuition may conflict
- Because of cognitive limitations, systematic biases and errors result from employing simpler rather than more complex cognitive strategies
- Evidence based medicine applies decision theory to clinical diagnosis

Problem solving

Diagnosis as selecting a hypothesis

The earliest psychological formulation viewed diagnostic reasoning as a process of testing hypotheses. Solutions to difficult diagnostic problems were found by generating a limited number of hypotheses early in the diagnostic process and using them to guide subsequent collection of data.[1] Each hypothesis can be used to predict what additional findings ought to be present if it were true, and the diagnostic process is a guided search for these findings. Experienced physicians form hypotheses and their diagnostic plan rapidly, and the quality of their hypotheses is higher than that of novices. Novices struggle to develop a plan and some have difficulty moving beyond collection of data to considering possibilities.

This is the fourth in a series of five articles

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